> the protein encoded thereby. The instant application does not disclose the biological role of this protein or its significance.

See Paper No. 42, page 3, section 7, paragraph 1.

Applicants respectfully disagree and traverse. Preliminarily, Applicants assert that the specification as filed discloses numerous biological roles for VIGF. For example, Applicants state on page 4, lines 13-15 and page 19, lines 7-9 of the specification that VIGF can be used to promote angiogenesis and proliferate vascular smooth muscle and endothelial cell production. Further, on page 28, lines 3-6, Applicants disclose that antibodies to the VIGF polypeptide can be used to diagnose vascular disease and neovascularization. Thus, contrary to the Examiner's statement, the instant application discloses several biological roles for the VIGF protein.

The Examiner had previously asserted that "there is no evidence of record to support any of the asserted utilities of the instant specification and one of ordinary skill in the art would not find any of the asserted uses of the specification specific, substantial and credible for the reasons of record." *See* Paper No. 35, page 3, first paragraph. Applicants responded by submitting the Aitkenhead *et al.* reference wherein the authors demonstrated a strong correlation between VIGF expression (therein referred to as ESM-1) and tumor angiogenesis. However, the Examiner alleges that the asserted utility is "not persuasive because the instant specification fails to teach which tumors the claimed invention would be useful for as a diagnostic," and because "[t]here is no evidence or showing on record that the claimed invention would prove useful in diagnosing tumors in any patient population." *See* Paper No. 42, pages 3-4, bridging paragraph. Applicants respectfully assert that the Examiner has failed to meet the burden of showing that a person of ordinary skill in the art would consider the asserted utility to be false because the Examiner has not presented evidence or reasoning to show that Aitkenhead does not support the Applicants' asserted utility.

The Examiner appears to question on several fronts whether Aitkenhead can be used to demonstrate the usefulness of VIGF as a marker for neovascularization and cancer. First, the Examiner cites that, while Aitkenhead showed VIGF upregulation in a number of renal cell carcinomas, "expression appeared to be somewhat higher in normal tissue in other samples." In asserting this position, the Examiner fails to acknowledge the <u>overall trend</u> of the results, instead focusing on a few data points that fall outside the overall trend. Indeed, 5 out of 14 samples in Fig. 5A (samples 1, 9, 12, 13, and 14) clearly demonstrate a <u>significant</u>

increase in VIGF expression (rows A & B) in kidney tumor tissue relative to normal kidney tissue. Further, Applicants observe one instance where VIGF expression is substantially higher in the tumor sample (sample 2). Applicants point out that VEGF expression (rows C & D) is also upregulated in the same renal tumor samples where VIGF is upregulated. This correlation of increased VIGF and VEGF expression in renal tumor samples is significant, as VEGF is a well-established marker for angiogenesis and cancer diagnosis and/or prognosis. Finally, Aitkenhead further discloses that similar correlations were observed for VIGF levels in tumors from breast, uterus, stomach and rectum. *See* Aitkenhead *et al.* (2002), page 166, first column. Thus, Applicants reiterate that Aitkenhead supports the asserted utility of using VIGF as a diagnostic marker for neovascularization and cancer.

Second, the Examiner quotes passages from Aitkenhead that allegedly cast doubt on the correlation between VIGF (ESM-1) expression and tumor angiogenesis. The Examiner states that "not all tumors up-regulate ESM-1," "ESM-1 may be a target of VEGF," and "ESM-1 may be an independent marker of tumor angiogenesis in some tissues." *See* Paper No. 42, page 4, lines 11-13. Applicants assert that the Examiner has taken the first statement ("not all tumors up-regulate ESM-1") out of context. Indeed, the second half of the sentence, which was not recited in the Office Action, claims that a there was a "strong correlation with the angiogenic marker VEGF, as well as with the degree of vascularity" and VIGF expression levels. Furthermore, whether VIGF acts downstream of VEGF or is independently regulated is irrelevant. As long as VIGF can be used to detect tumor neovascularization as asserted in the specification, then the utility requirement is satisfied. Thus, based on the evidence provided, Applicants maintain that Aitkenhead allows one of ordinary skill in the art to conclude that VIGF would be useful as a marker for angiogenesis and cancer.

Third, the Examiner appears to find Aitkenhead deficient because the reference does not disclose a molecular mechanism that links VIGF to angiogenesis. In response, Applicants assert that understanding how or why an invention works is not a legal requirement. *See, e.g.*, *Newman v. Quigg*, 11 U.S.P.Q.2d 1340, 1345 (Fed. Cir. 1989); *Diamond Rubber Co. v. Consolidated Rubber Tire Co.*, 220 U.S. 428, 435-36, 55 L. Ed. 527, 31 S. Ct. 444 (1911); *Fromson v. Advance Offset Plate Inc.*, 720 F.2d 1565, 1570, 219 U.S.P.Q. (BNA) 1137, 1140 (Fed.Cir. 1983). In the instant specification, Applicants have identified that the nucleic acids and proteins of the present invention can be used as a cancer diagnostic, and now Applicants have provided third party data in support of that diagnostic utility.

Notwithstanding the credibility of the Aitkenhead reference, the Examiner further alleges that Applicants have failed to demonstrate that VIGF would be a diagnostic marker for cancers in general. *See* Paper No. 42, page 5, line 6. Applicants submit herewith another reference in support of VIGF's utility as a diagnostic marker for angiogenesis and cancer. van't Veer *et al.* have identified VIGF (ESM1 in the van't Veer reference) as a gene that is significantly upregulated in breast cancers with poor prognosis signatures. *See* van't Veer *et al.* (2002) Nature 415:530-536 (submitted herewith as Exhibit A) at pg. 534, left column, first full paragraph. This further supports Aitkenhead's observation that VIGF expression is elevated in breast cancer.

In addition, regarding the Examiner's first assertion (*supra*), Applicants assert that, at the time the application was initially filed, one of ordinary skill in the art would have recognized the correlation between angiogenesis and cancers, specifically solid tumors. Hence, the use of VIGF to diagnose cancers in general would be reasonable. Indeed, VIGF expression is elevated in six unrelated cancers based on the teachings of Bechard *et al.* and Aitkenhead *et al.*: lung, kidney, stomach, breast, uterine and rectal. These six cancers account for a significant number of all cancers. Five of the ten most frequently occurring cancers from 1995 to 1999 are likely to express increased levels of VIGF. *See* Table 3, Edwards *et al.* (2002) Cancer 94(10):2766-2792 (submitted herewith as Exhibit B). Furthermore, in data from the National Cancer Institute (NCI) for 2003, deaths from these six cancers represent 64% of all cancer deaths from solid tumors in women, while new incidences for these six cancers account for 62% of all new cancer cases reported for solid tumors in women.[1] *See* SEER Cancer Statistics Review, 1975-2000, (2003) National Cancer Institute, available online at http://seer.cancer.gov/csr/1975_2000 (submitted herewith as Exhibit C). Thus, Applicants have provided new evidence that supports the asserted utility of VIGF as a diagnostic marker for cancers in general.

The Examiner asserts that the specification "fails to suggest the use of the claimed invention for the diagnosis of renal tumors" and "fails to assert the utility of diagnosing lung tumors." *See* Paper No. 42, page 4, lines 18-19 and page 5, lines 9-10. The Examiner further states that the use for diagnosis of renal and lung tumors would be specific, substantial, and credible. Applicants point out that the specification explicitly identifies both the lung and

[1] This analysis specifically focuses on the cancer statistics data for women since two of the six cancers for which published data on VIGF expression are available occur predominantly in women, *i.e.*, uterine and breast cancers.

kidney as tissues where VIGF expression was detected. One of ordinary skill in the art could reasonably conclude that VIGF would be useful in the diagnosis of both lung and kidney cancer since the specification asserts that altered levels of VIGF may be indicative of such disorders. Therefore, based on the disclosure of the specification and the Examiner's own admission, Applicants have provided a specific, substantial and credible utility for the claimed invention.

Finally, the Examiner alleges that Applicants' asserted utility as a cancer diagnostic is "complicated by Bechard et al. which teaches that septic patients have elevated ESM-1." *See* Paper No. 42, page 5, line 1. Applicants respectfully point out that sepsis and cancer are two significantly different diseases with distinct characteristics. It is highly unlikely that a medical professional would erroneously diagnose a septic patient with cancer or vice versa, as both sepsis and cancer have hallmark characteristics that are easily distinguishable. Thus, Applicants maintain that VIGF's utility as a cancer diagnostic is not precluded by the increased level of VIGF in septic patients.

In view of the above arguments, Applicants have provided evidence and reasoning which supports their assertion of a specific, substantial, and credible utility. While several specific utilities have been disclosed in the specification, only one credible assertion of utility is required. *See, e.g., Raytheon v. Roper*, 724 F.2d 951 (Fed. Cir. 1983). In particular, Applicants have provided evidence that the polypeptides and/or antibodies raised against the polypeptide of the instant application would be useful as a diagnostic marker for neovascularization and cancer, in particular lung and kidney cancer. Thus, the utility asserted in the specification for Human Vascular IBP-Like Growth Factor Polynucleotides is indeed specific, substantial and credible. Accordingly, Applicants respectfully submit that the rejection of claims 54-67, 75-92, 102-107, 115-119, and 122-175 under 35 U.S.C. § 101 should be reconsidered and withdrawn.

III. Rejection Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 54-67, 75-92, 102-107, 115-119, and 122-175 under 35 U.S.C. § 112, first paragraph, for the reasons set forth above.

Applicants respectfully disagree and traverse. For the reasons discussed above in response to the rejection under 35 U.S.C. § 101, the claimed invention is supported by a specific, substantial and credible asserted utility. The Examiner "should not impose a 35